meta-Selective C–H arylation of phenols via regiodiversion of electrophilic aromatic substitution

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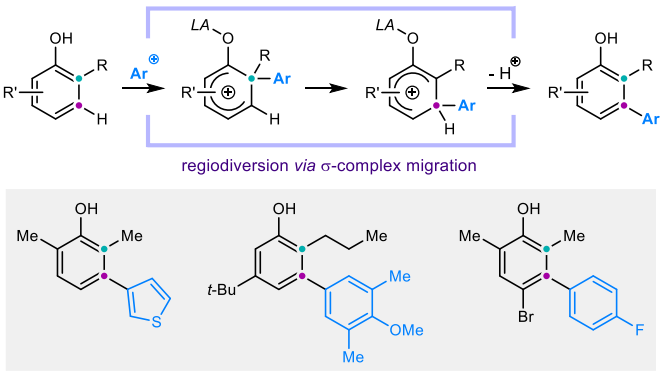


Abstract

Electrophilic aromatic substitution (EAS) is among the most widely used mechanistic manifolds in organic chemistry. Access to certain substitution patterns is, however, precluded by intrinsic and immutable substituent effects that ultimately restrict the diversity of benzenoid chemical space. Here we demonstrate that the established regioselectivity of EAS can be overcome simply by diverting the key σ-complex intermediate towards otherwise

inaccessible substitution products. This 'regiodiversion' strategy is realized through the development of a general and concise method for the *meta*-selective C–H arylation of sterically congested phenols. Consisting of a Bi(V)-mediated electrophilic arylation and a subsequent aryl migration/rearomatization, our process is orthogonal to conventional C–H activation and cross-coupling approaches, and does not require prefunctionalization of the substrate. Mechanistically informed applications in synthesis showcase its utility as a versatile and enabling route to highly functionalized, contiguously substituted aromatic building blocks that defy synthesis *via* existing methods.

Main Text

Electrophilic aromatic substitution (EAS) is a cornerstone of chemical synthesis. It has special historical significance, being the field in which much of organic mechanism theory was developed during the previous century.[1] It also has special contemporary significance as the most widely-used method for functionalizing benzenoid rings, which feature in over 45% of FDA-approved pharmaceuticals,[2] 59% of FDA-approved veterinary medicines,[3] and one third of the *ca* 10 million distinct chemical entities that have been synthesized to date.[4]

While the highly predictable and largely immutable selectivity associated with EAS underpins synthetic route design,[5,6] it also inherently limits the diversity of accessible benzenoid chemical space. In particular, the ability of an electron-donating substituent to both activate an aromatic ring towards EAS, and to direct substitution *ortho* or *para* to itself (Fig. 1a), has led to relatively few benzenoid substitution patterns now dominating contemporary commercial catalogs, academic repositories, and marketed drugs (Fig. 1b).[7–9] The resulting

bias towards 1,4 and 1,2,4 relationships is especially exaggerated in benzenoids featuring very strongly electron-donating substituents, such as phenols (Fig. 1c). A strategy that overcomes the rigid regioselectivity of EAS would therefore expedite the preparation of benzenoids that defy synthesis *via* existing methods and would ultimately expand the horizons of accessible chemical space.

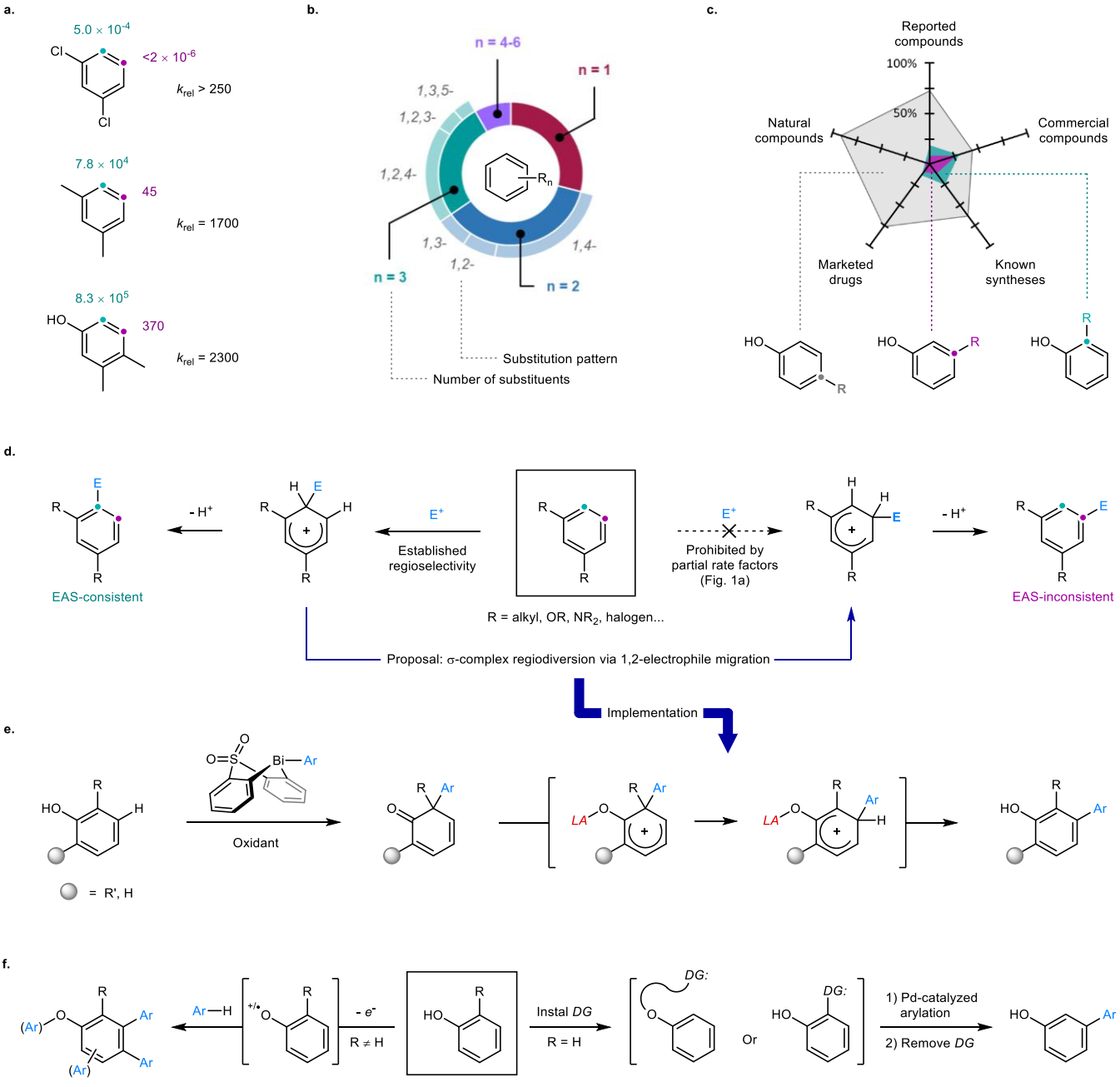


Fig. 1. Origins, consequences, and diversion of EAS regioselectivity. a, High relative rate differentials confer predictable and immutable chemo- and regioselectivity on EAS. Values in teal and purple represent partial rate factors for EAS, relative to benzene.[1] **b**, EAS-consistent substitution patterns currently dominate benzenoid chemical space, which spans 2.8×10^7 compounds (donut chart: inner shell represents percentage distribution of benzenoids with different total numbers of substituents (n) across known benzenoid space; outer shell

represents isomeric composition for a given number of substituents). **c**, Well- established electronic effects lead to especially biased regioisomer distributions for benzenoids bearing strongly electron-releasing substituents. This trend is illustrated for the 3.8×10^4 known monosubstituted phenols (radar plot: each axis represents the percentage distribution of isomeric monosubstituted phenols across the stated attribute). **d**, The mechanistically imposed regioselectivity of EAS is a fundamental tenet of organic chemistry that cannot be directly reversed; we propose to circumvent this challenge by interception and diversion of the key, regiochemically-favored σ-complex. **e**, *meta*-Selective C–H arylation of phenols as a testbed for the EAS-regiodiversion concept. **f,** Our mechanistically-distinct solution to the *meta*-arylation challenge offers complementary scope to existing strategies based on oxidative coupling or directed C–H functionalization, which are typically limited by poor selectivity and the need for electron rich partners, or multi-step installation / removal of directing groups and incompatibility with *ortho* / *para* substituents, respectively. k_{rel}, relative rate; R, alkyl, aryl or heteroatom substituent; E^+, electrophile; Ar, (hetero)aryl; LA, Lewis acid; DG, Lewis-basic directing group.

We hypothesized that a formal inversion of EAS regioselectivity may be possible *after* the initial dearomatization, but prior to rearomatization (Fig. 1d). Specifically, if the regiochemically-favoured σ-complex could be prevented from evolving directly to the expected EAS product, 1,2-electrophile migration would generate a new and otherwise-inaccessible σ-complex. Rearomatization of this inherently disfavoured isomer would ultimately afford an electrophilic substitution product featuring valuable and underrepresented regiochemistry.

To test this hypothesis, we turned to the electrophilic arylation of phenols. The reactivity of these abundant and biorenewable building blocks[10] is dominated by EAS *ortho* or *para* to the hydroxyl (Fig. 1c),[1,11] so the ability to divert substitution to the *meta* position would be especially valuable. We proposed that application of the oxidative bismuth-mediated electrophilic C–H arylation protocol recently developed in our laboratory[12] to a 2-substituted phenol would give direct access to a dearomatized 2,4-cyclohexadienone (Fig. 1e).[13–16] Formal reconstitution of the corresponding EAS-consistent σ-complex intermediate by addition of a Brønsted or Lewis acid would then initiate a Dienone-Phenol rearrangement[17] in which 1,2-aryl migration generates the regioisomeric, EAS-*inconsistent* σ-complex, and ultimately a densely functionalised *meta*-arylated phenol.

Our proposed strategy thus hinges on the success of two components: initial synthesis of the requisite 2,4-cyclohexadienones, and their subsequent rearrangement / rearomatization. While electrophilic dearomatization of phenols is readily achieved by halogenation, amination, oxygenation, and alkylation,[18,19,20,21,22,23,24,25,26] arylative dearomatization is less well established. This is particularly true for the arylative synthesis of 2,4-cyclohexadienones, which requires selective addition to the *ortho* position of the phenol substrate. Existing methods include oxidative coupling processes that proceed through initial chemical[27,28,29] or electrochemical[30] oxidation of the phenol to a phenoxy radical or phenoxonium cation, which is then trapped by an electron rich arene (Fig. 1f). However, while elegant in its simplicity, this biomimetic approach is limited to only a handful of examples, requires electron rich partners and excess arene, affords modest regioselectivity with respect to both components, and suffers from poor chemoselectivity (C–H *vs* O–H arylation, cross *vs* homocoupling, and over-oxidation). In addition, spontaneous Dienone-Phenol rearrangement occurs in the majority of

examples, preventing isolation of the desired 2,4-cyclohexadienone and ultimately resulting in uncontrolled polyarylation that erodes the yield of the *meta*-arylated product. In contrast, while closed-shell manifolds based on ligand coupling at I(III),[31,32] Pb(IV)[33,34] or Bi(V)[13–16] typically allow for isolation of the intermediate 2,4-cyclohexadienone, they are similarly limited by poor selectivity (C_{ortho} vs C_{para} vs *O*), low yields, and / or impracticality (including reliance on neurotoxic aryllead reagents or explosive $BiPh_5$[35]).

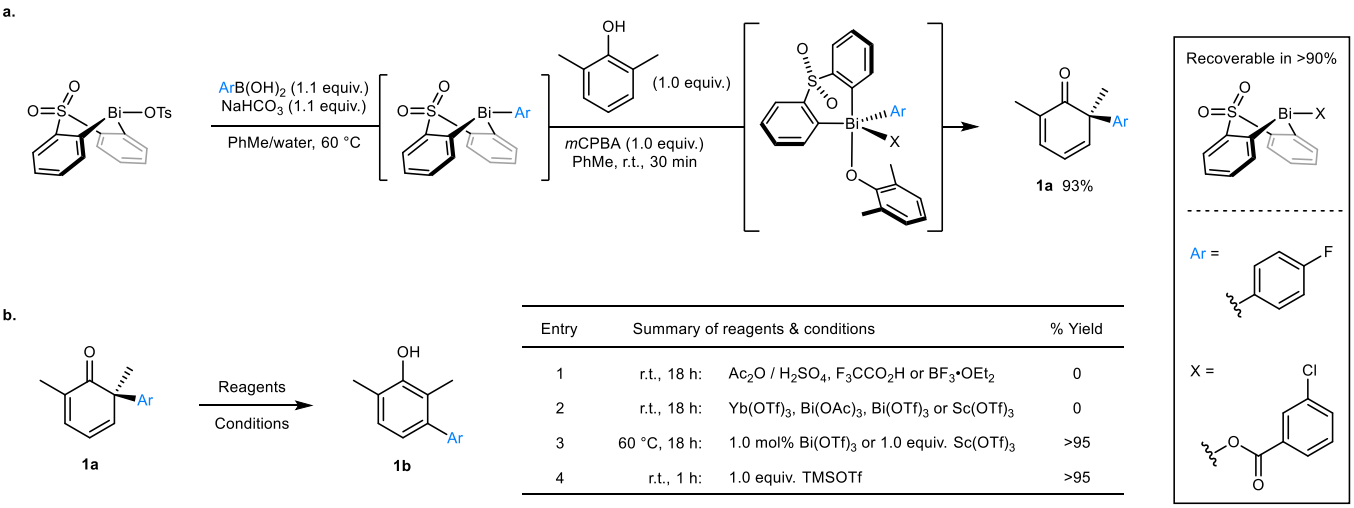
The Dienone-Phenol rearrangement – on which the second step of our proposed strategy depends – is well known for the migration of alkyl substituents,[17,36] especially in an intramolecular setting and/or from 2,5-cyclohexadienones. By comparison, the analogous migrations of aryl groups are far less well developed, particularly from 2,4-cyclohexadienones. Indeed, the most notable examples are the spontaneous rearrangements that accompany Pappo's elegant oxidative coupling methodology,[27,28] and which almost always lead to polyarylation (only one example of selective monoarylation is reported, giving 32% yield[28]). However, the extensive precedent for 1,2-aryl migrations along acyclic frameworks[37] suggests that if a robust arylative method for 2,4-cyclohexadienone synthesis could be developed, then application of this migratory manifold to cyclic frameworks should be viable.[38,39,40]

In addition to circumventing the regioselectivity that defines EAS, realization of our proposed regiodiversion strategy would provide a powerful tool for the *meta*-selective C–H arylation of phenols. The handful of methods currently available for the controlled *meta*-arylation of phenols exploit Pd-mediated C–H activation and achieve regioselectivity by installation of a Lewis-basic directing group at[41,42] or adjacent to[43,44,45,46] the phenolic hydroxyl (Fig. 1f). In addition to requiring prefunctionalization of the substrate, these strategies do not tolerate

pre-existing *ortho* or *para* substituents, and therefore cannot provide access to densely functionalized phenols featuring contiguous substitution patterns (*e.g.*, 2,3 or 2,3,4 substitution). Similar steric limitations attend alternative methods based on C–H borylation – which is selective towards unhindered C–H bonds[47] and typically low-yielding for unprotected phenols (33-66%)[48–50] – or tandem oxidative Heck coupling/dehydrogenation of cyclohexenones.[51] In contrast, by virtue of its mechanistically distinct mode of operation, our approach (Fig. 1e) provides concise access to contiguously-substituted *meta*-aryl phenols and is therefore complementary to existing *meta*-arylation methods.

Results and Discussion

Reaction development. At the outset we established that our oxidative bismuth-mediated electrophilic arylation[12] could be used to convert an *ortho*-substituted phenol to the corresponding σ-complex analog.[13–16] Thus, following optimization, 2,6-dimethylphenol was converted to dienone **1a** in excellent isolated yield *via* telescoped B-to-Bi transmetallation, oxidation and arylation (Fig. 2a). This process represents a rare example of an intermolecular arylative dearomatization,[18,19,20,21,22,23] and exhibits unrivalled economy with respect to the stoichiometry of both the phenol and the aryl group being transferred.[13–16,27,28,29,30,31,32,33,34] The bench-stable bismacycle precursor can be prepared conveniently on decagram scales without chromatography, and can be recovered and recycled in >90% yield at the end of the arylation sequence (see Fig. 4b and Supplementary Section 4). The efficiency of this recovery process constitutes a loss of <10 mol% of the bismacycle through the whole process, representing comparable economy to catalytic *meta*-arylation protocols that typically employ high Pd loadings (10-15 mol%).[41,42,44]



Entry	Summary of reagents & conditions		% Yield
1	r.t., 18 h:	Ac_2O / H_2SO_4, F_3CCO_2H or BF_3•OEt_2	0
2	r.t., 18 h:	$Yb(OTf)_3$, $Bi(OAc)_3$, $Bi(OTf)_3$ or $Sc(OTf)_3$	0
3	60 °C, 18 h:	1.0 mol% $Bi(OTf)_3$ or 1.0 equiv. $Sc(OTf)_3$	>95
4	r.t., 1 h:	1.0 equiv. TMSOTf	>95

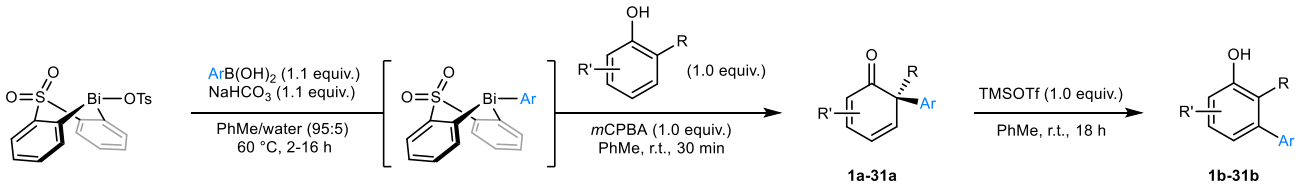
Fig. 2. Proof of principle and reaction development. a, Bismuth-mediated electrophilic arylation provides modular access to EAS-consistent σ-complex analogs. Starting from a single bismacycle precursor, B–to–Bi transmetallation, oxidation and arylation can be performed as a single telescoped operation without exclusion of air or moisture, and the bismacyclic scaffold can be recovered as the corresponding *meta*-chlorobenzoate. Yields are of isolated, purified material. **b**, σ-Complex regiodiversion expedites *meta*-selective arylation of sterically congested phenols. Optimization of 1,2-aryl migration was performed using isolated dienone **1a** in anhydrous $CDCl_3$ or toluene, with yields determined by ^{19}F NMR spectroscopy *vs* internal standard (4,4'-bis(trifluoromethyl)biphenyl); see Supplementary Section 3 for full experimental details. *m*CPBA, *meta*-chloroperbenzoic acid; Ac, acetyl; Tf, triflyl; TMS, trimethylsilyl.

Exposure of dienone **1a** to a range of Brønsted acids failed to initiate the desired 1,2-aryl migration (Fig. 2b, entry 1; see also Supplementary Table 1), despite similar conditions having been employed in related rearrangements.[36,52] While a range of Lewis acids derived from boron or oxophilic metal triflates proved similarly unsuccessful at ambient temperature (entry

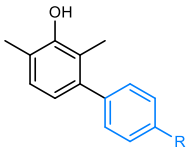
2), both $Bi(OTf)_3$ and $Sc(OTf)_3$ promoted the rearrangement of dienone **1a** to *meta*-arylphenol **1b** at raised temperatures and after extended durations (entry 3). In contrast, *meta*-arylphenol **1b** is formed rapidly, in quantitative yield, and with excellent purity upon treatment with trimethylsilyl triflate (TMSOTf) at ambient temperature (entry 4). Therefore, in combination with the economical stoichiometries of reagents used in dienone synthesis and the recoverability of the bismacycle, our strategy represents an atom efficient route to *meta*-arylated phenols (see Supplementary Section 4 for additional discussion).

Reaction scope. A broad array of aryl moieties can be installed using our methodology (Table 1), with high yields achieved for arylboronic acids bearing electron donating and withdrawing functionality (**1-10**) or featuring *ortho* substitution (**11**, **12**). Notably, the scope includes synthetically useful bromoaryl (**5**) and protolytically-sensitive polyfluoroaryl boronic acids (**11**),[53] rendering it complementary to conventional cross-coupling. Heterocycles are also well tolerated in both the arylation step and, with the exception of a Lewis-basic pyridine, the migration step (**13**-**15**). The resistance of dienone **15a** to rearomatization is consistent with our qualitative experimental observation that the rate of 1,2-migration decreases for electron-poor aromatics; the origins of this trend are addressed quantitatively in the subsequent discussion of reaction mechanism.

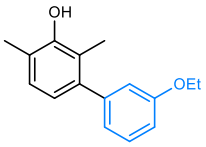
Table 1. Scope of *meta*-selective phenol arylation.[a]



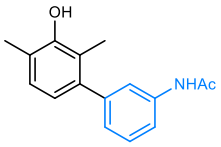
1a-31a **1b-31b**



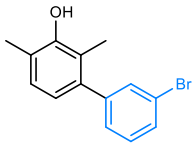
R = F	**1a** 93%	**1b** 96%
OMe	**2a** 69%	**2b** 92%
Me	**3a** 73%	**3b** 91%
H	**4a** 75%	**4b** 89%
Br	**5a** 84%	**5b** >99%
CF_3	**6a** 72%	**6b** >99%



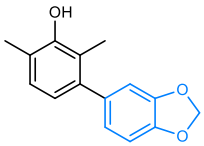
7a 76% **7b** 94%



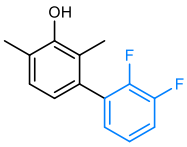
8a 76% **8b**[b] 90%



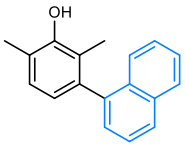
9a 82% **9b** 94%



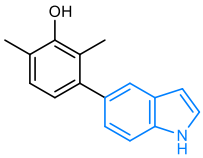
10a 70% **10b**[c] 94%



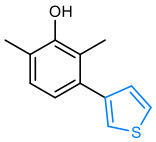
11a 67% **11b** 79%



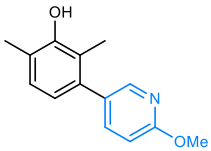
12a 59% **12b** 72%



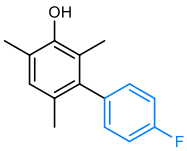
13a 57% **13b**[c] 83%



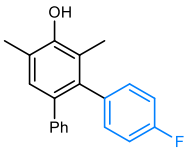
14a 72% **14b** 93%



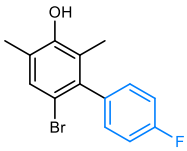
15a 75% **15b** 0%



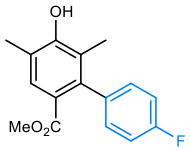
16a 81% **16b** 96%



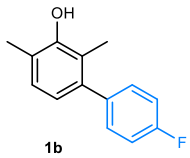
17a 81% **17b** 95%



18a 71% **18b** 91%



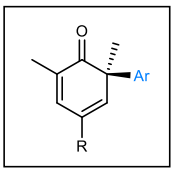
19a 82% **19b** 70%



1b

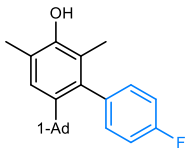
from R = 1-Ad >99%
t-Bu >99%

TMSOTf (1.0 equiv.)
1,2-Aryl migration &
retro Friedel-Crafts

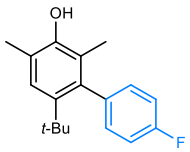


R = 1-Ad **20a** 87%
t-Bu **21a** 89%

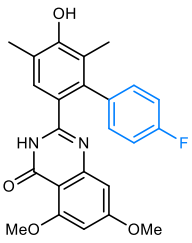
20 mol% $Bi(OTf)_3$
20 mol% NEt_3



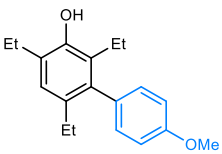
20b[c] 81%



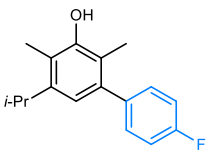
21b[c] 85%



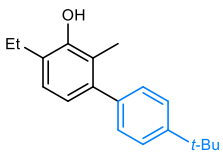
22a[b] 87% **22b**[d] 93%
⇒ *apabetalone*



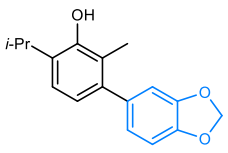
23a 83% **23b** 83%



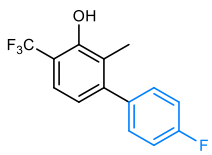
24a[e] 41% **24b** 93%



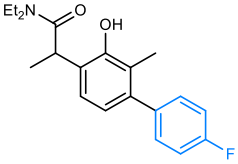
25a 64% **25b** 83%
1:1 r.r.



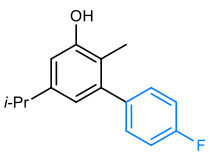
26a 68% **26b**[c] 97%
2.5:1 r.r.



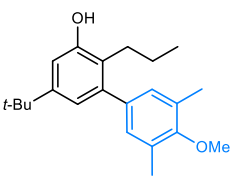
27a 61% **27b** 90%



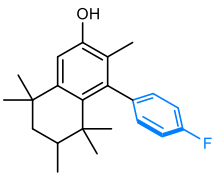
28a 52% **28b**[f] 83%



29a[g] 49% **29b** 84%



30a 59% **30b**[d] 84%



31a 81% **31b** 96%
⇒ *musk tonalid*

[a] Yields are of isolated, purified materials (single regioisomers, unless stated otherwise); regioisomer ratios (r.r.) were determined by ^{19}F and/or ^{1}H NMR spectroscopic analysis prior to purification. [b] Performed in $CHCl_3$ solvent using isolated aryl bismacycle. [c] Modified migration conditions for (potentially) acid-sensitive substrates: $Bi(OTf)_3$ (20 mol%) and NEt_3 (20 mol%) replace TMSOTf, 60 °C. See Supplementary Section 3 for further discussion. [d] 2.0 equiv. TMSOTf. [e] Yield of single regioisomer following purification (1:1 r.r. prior to purification, as determined by ^{1}H NMR spectroscopy). [f] Migration performed at 60 °C. [g] Yield of single regioisomer following purification (1.3:1 r.r. prior to purification, as determined by ^{1}H NMR spectroscopy). 1-Ad, 1-adamantyl.

The generality of our strategy extends equally to the phenol substrate. Both the initial dearomatization and the subsequent aryl migration proceed efficiently for diverse 2,6-dimethylphenols, providing regiocontrolled access to highly congested, polysubstituted phenols in excellent yields (**1**, **16**-**22**). Of particular note, migration occurs smoothly to place the aryl group adjacent to even very sterically demanding *tert*-alkyl substituents (**20b**, **21b**); by judicious choice of the migration conditions, TfOH-mediated protodealkylation[1] of the initial rearrangement product can either be suppressed (**20a** → **20b**; **21a** → **21b**) or promoted (**20a**/**21a** → **1b**). In addition, the reaction tolerates both Lewis basic functionality – as illustrated by the synthesis of **22b**, the precursor to an arylated analog of the BET kinase inhibitor apabetalone (RVX-208)[54] – and increased hindrance at the site of arylation (**23**).

When applied to non-symmetrical phenols, the initial bismuth-mediated arylation exhibits regioselectivity consistent with its electrophilic nature (see Supplementary Section 4 for additional data and discussion).[12] Thus, modest selectivity is observed where the *ortho*

positions are sterically and electronically similar (**24a**-**26a**), whereas complete selectivity is observed for more highly differentiated substrates (**27a**, **28a**). Dearomatization can also be achieved in good to excellent yields for non-symmetrical phenols bearing a single *ortho* substituent (**29a-31a**). For these substrates, arylation *ipso* to an alkyl substituent competes effectively with arylation *ipso* to hydrogen (compare **24a** and **29a**), and complete regioselectivity can be conferred by distal substiuents (**30a**, **31a**). Our methodology therefore provides access to valuable polysubstituted benzenoids decorated with four (**25**-**30**) or five (**31**) unique substituents, where the final modification defies established EAS selectivity and C–H functionalization logic. This is illustrated in the facile synthesis of **31b**, a derivative of the fragrance musk tonalid (fixolide).

By harnessing and diverting EAS, our *meta*-selective arylation strategy not only demonstrates the viability of an underexplored reactivity concept, but also enjoys important practical benefits that distinguish it from other *meta*-arylation protocols. First, our interrupted arylation / migration process precludes polyarylation of the substrate, and therefore allows high yields to be achieved while using economic stoichiometries of coupling partners. Second, our bismacycle-based system confers complete *ortho*-selectivity with respect to the initial arylation of the phenol substrate, and regiospecificity with respect to the aryl moiety being transferred. And third, while it cannot be used to access 2,6-unsubstituted *meta*-aryl phenols, our approach is compatible with pre-existing *ortho* and *para* substitution, thereby expediting the synthesis of contiguously functionalized phenols and providing a complement to Pd-catalyzed methods.

Reaction mechanism and synthetic applications. Having established the broad scope of our *meta*-arylation methodology, we sought to better understand the mechanism and electronic demands of the key regiodiversion process (Fig. 3), and its wider utility in target synthesis (Fig. 4). Pairwise intermolecular competition between dienones indicated that the relative migratory aptitude of electronically-differentiated aryl moieties varies by up to 4 orders of magnitude (Fig. 3a), consistent with our qualitative observation that the absolute rate of migration also depends heavily on electronic factors. Together, these trends in absolute and relative rates indicate that aryl migration is both selectivity- and rate-determining, which requires that initial Lewis acid activation of the dienone be rapid and reversible.

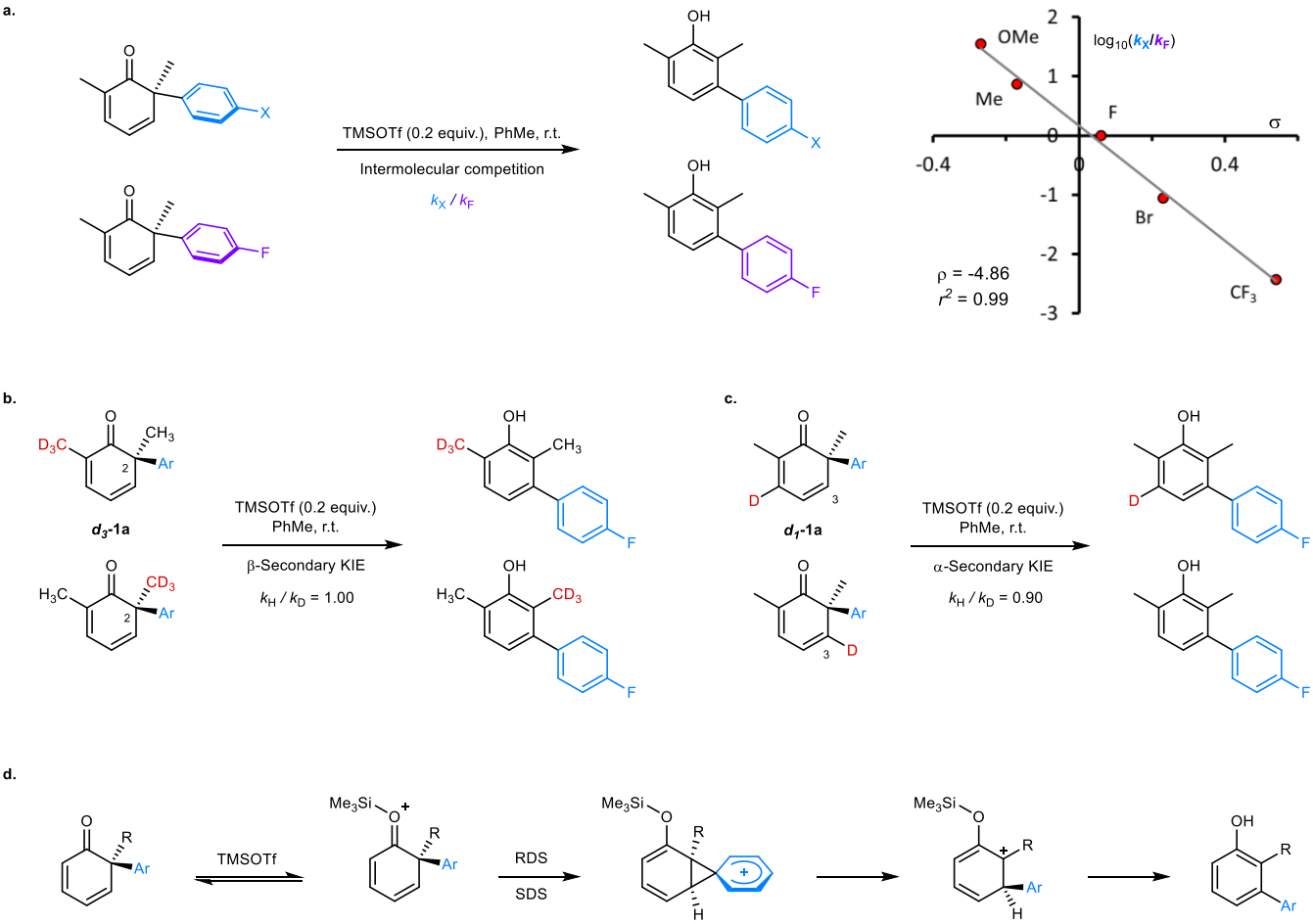


Fig. 3. Mechanistic analysis of σ-complex regiodiversion. a, Pairwise intermolecular competition between cyclohexadienones indicates that 1,2-aryl migration is accompanied by a significant increase in partial positive charge (ρ = -4.86). The Hammett plot is constructed from measurements of single experiments; the line of best fit is calculated by linear least squares regression, and r^2 is the square of the Pearson product moment correlation coefficient. **b**, No appreciable β-secondary kinetic isotope effect (k_H/k_D = 1.00) is observed during competitive rearomatization of deuteromethyl isotopomers ***d*$_3$-1a**. **c**, An α-secondary kinetic isotope effect (k_H/k_D = 0.90) is observed during competitive rearomatization of isotopomers ***d*$_1$-1a**. **d**, Key mechanistic features of the regiodiversion process, which is proposed to proceed via a phenonium ion intermediate. Product distributions were determined by ^{1}H NMR spectroscopic analysis of unpurified reaction mixtures. σ, Hammett substituent constant; ρ, Hammett reaction constant; D, deuterium (^{2}H); RDS, rate determining step; SDS, selectivity determining step.

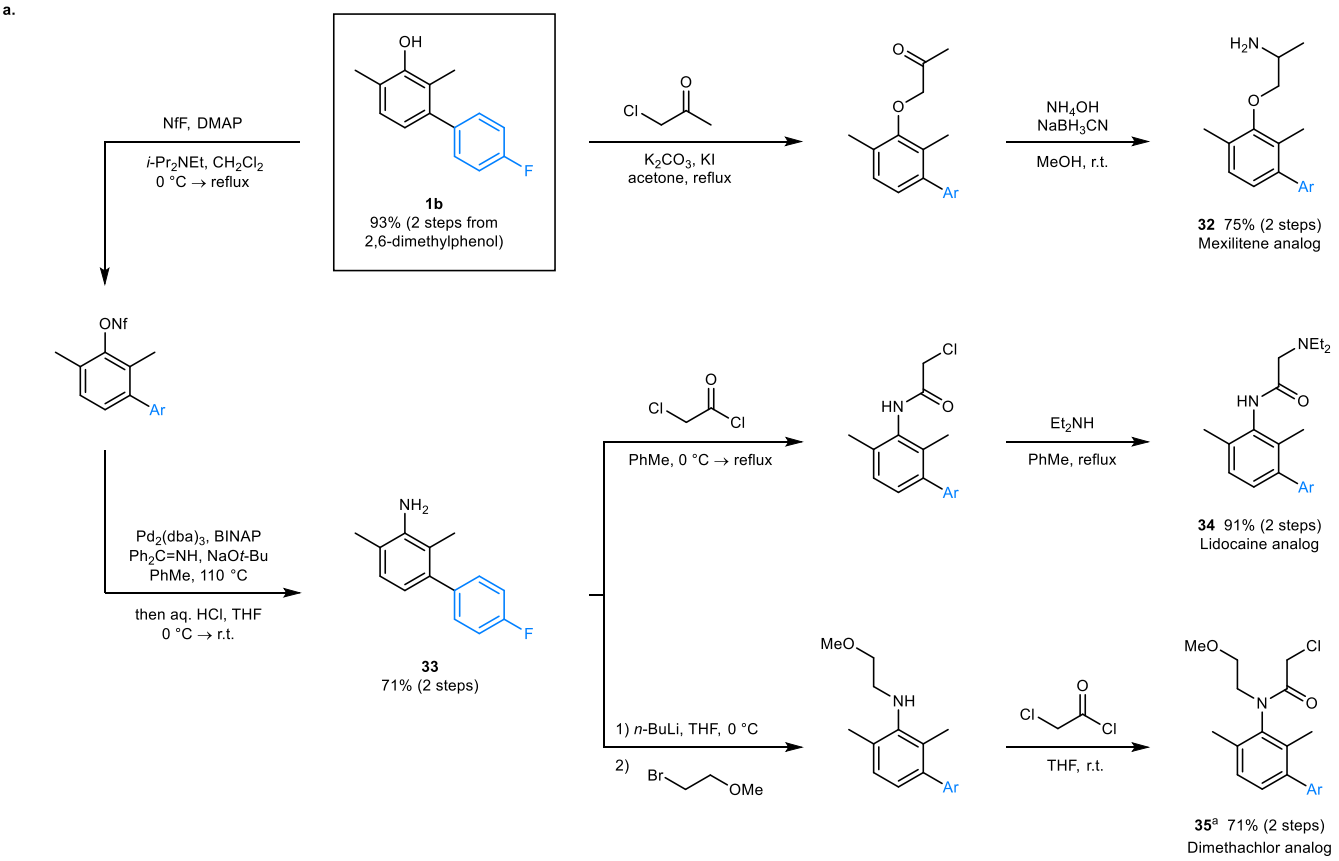
A Hammett plot of these competition data against standard σ values gives excellent correlation and a large, negative reaction constant (ρ = –4.9). The similarly large values reported for 1,2-aryl migrations in Wagner-Meerwein (ρ = –3.7)[55] and pinacol-type rearrangements (ρ = –6.9)[56] have been interpreted as accumulation of substantial positive charge on the migrating group. It is therefore now apparent why the 3-pyridyl moiety in dienone **15a** does not migrate (Table 1): not only is the pyridyl ring inherently more electron-poor than a typical benzenoid (σ_p(3-pyridyl) = 0.25; σ_p(phenyl) = –0.01),[57] but protonation or formation of a trimethylsilyl adduct[58] would deactivate it further (σ_p(3-pyridinium) ≥ 2).[59]

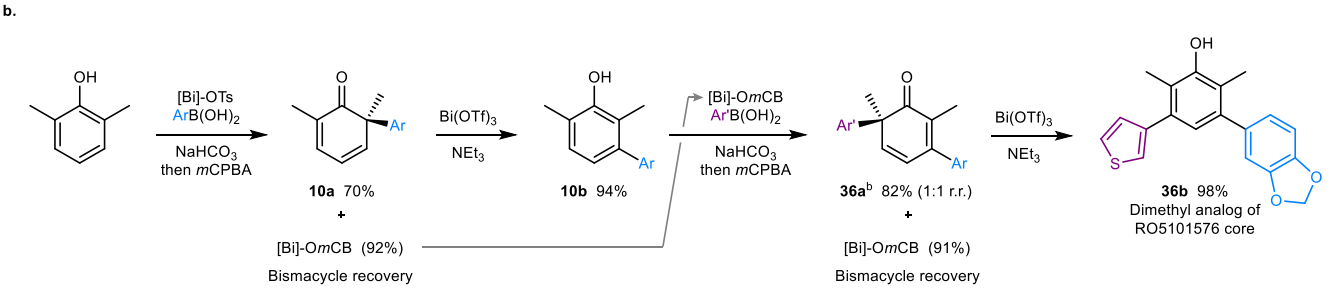
Insight into the extent of bond formation and scission that occurs during aryl migration was provided by deuterium kinetic isotope effects (KIEs). Intermolecular competition between two isotopomers of ***d*$_3$-1a** does not yield a detectable inverse β-secondary KIE (SKIE; k_H/k_D = 1.00, Fig. 3b). This is consistent with minimal hyperconjugation developing between the migration origin (C2 of the dienone) and the adjacent methyl substituent, which in turn suggests that appreciable positive charge does not develop at C2 during the selectivity determining step. The small β-SKIE value observed in related alkyl migrations (k_H/k_D = 0.92) has been interpreted similarly,[52] and is juxtaposed with the large β-SKIE value expected where hyperconjugation to an adjacent carbocation is possible (*e.g.*, in solvolysis of the *tert*-butyl carbocation: k_H/k_D = 1.52 per methyl).[60] As such, we propose that significant bonding character persists between C2 and the aryl moiety during the selectivity determining step of aryl migration.

In contrast, intermolecular competition between two isotopomers of ***d*$_1$-1a** gives a substantial inverse α-secondary KIE (k_H/k_D = 0.90, Fig. 3c). This value is consistent with increasing sp^3 character at C3 of the dienone (*cf*. σ-complex formation in conventional EAS[1]), and suggests that significant C3-aryl bonding develops in the selectivity determining step of aryl migration. The absence of a primary KIE suggests that migration is irreversible and selectivity-determining, and that C3-H/D bond cleavage is not concerted with the migration process.

Taken together, these KIE and Hammett data are consistent with migration occurring through rate-limiting and selectivity-determining formation of a phenonium ion intermediate (Fig. 3d),[61] as has been proposed for Wagner-Meerwein shifts of aryl substituents along aliphatic skeletons.[55] Hence our regiodiversion of EAS involves dearomatization of not one, but two aryl groups, with formal transfer of positive charge between them.

The ability to formally divert electrophilic arylation in this way provides facile access to unprecedented, *meta*-arylated analogs of commercial pharmaceuticals and agrochemicals (Fig. 4a). For example, from phenol **1b**, a sequence of *O*-alkylation and reductive amination furnishes an analog of the antiarrhythmic mexiletine (**32**). Alternatively, aminodeoxygenation of phenol **1b** provides *meta*-arylated aniline **33**, which serves as a precursor to analogs of the anaesthetic lidocaine (**34**) and the herbicide dimethachlor (**35**). Notably, existing methods for the *meta*-selective arylation of aniline derivatives do not tolerate pre-existing *ortho* substituents,[42,62–64] so the ability to convert from phenol **1b** to aniline **33** represents a powerful and enabling route to this otherwise inaccessible motif.


a.
NfF, DMAP
i-Pr2NEt, CH2Cl2
0 °C → reflux
1b
93% (2 steps from
2,6-dimethylphenol)
K2CO3, KI
acetone, reflux
NH4OH
NaBH3CN
MeOH, r.t.
32 75% (2 steps)
Mexilitene analog
Pd2(dba)3, BINAP
Ph2C=NH, NaOt-Bu
PhMe, 110 °C
then aq. HCl, THF
0 °C → r.t.
33
71% (2 steps)
PhMe, 0 °C → reflux
Et2NH
PhMe, reflux
34 91% (2 steps)
Lidocaine analog
1) n-BuLi, THF, 0 °C
2)
THF, r.t.
35a 71% (2 steps)
Dimethachlor analog


b.
[Bi]-OTs
ArB(OH)2
NaHCO3
then mCPBA
10a 70%
+
[Bi]-OmCB (92%)
Bismacycle recovery
Bi(OTf)3
NEt3
10b 94%
[Bi]-OmCB
Ar'B(OH)2
NaHCO3
then mCPBA
36ab 82% (1:1 r.r.)
+
[Bi]-OmCB (91%)
Bismacycle recovery
Bi(OTf)3
NEt3
36b 98%
Dimethyl analog of
RO5101576 core

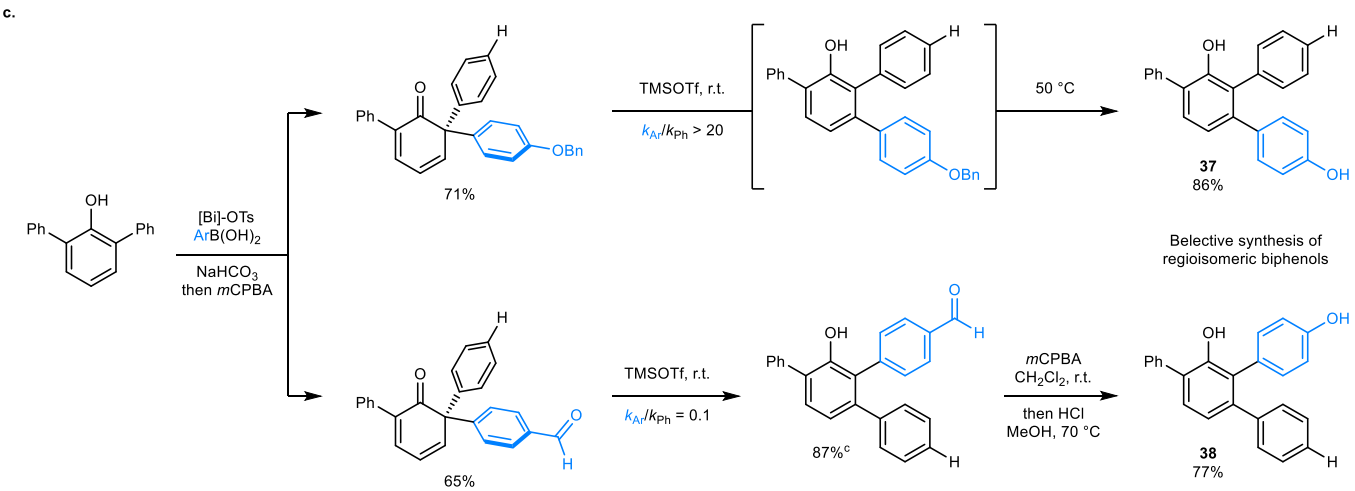

c.
[Bi]-OTs
ArB(OH)2
NaHCO3
then mCPBA
71%
TMSOTf, r.t.
kAr/kPh > 20
50 °C
37
86%
Belective synthesis of
regioisomeric biphenols
65%
TMSOTf, r.t.
kAr/kPh = 0.1
87%c
mCPBA
CH2Cl2, r.t.
then HCl
MeOH, 70 °C
38
77%

Fig. 4. Synthetic applications of *meta*-selective C–H arylation. a, *meta*-Selective arylation of *ortho*-substituted phenols enables the concise synthesis of novel analogs of pharmaceuticals and agrochemicals (**32**, **34**, **35**). **b**, Sequential *meta*-selective arylation / bismacycle recovery facilitates the modular synthesis of non-symmetrical 3,5-diarylphenol **36b**. The synthesis of **10a** and **36a** was performed according to the conditions illustrated in Table 1. **c**, Mechanistically-informed route design expedites highly selective synthesis of biphenol isomers **37** and **38**. The initial arylations were performed according to the conditions illustrated in Table 1. Yields are of isolated, purified materials (single regioisomers). [a] Yield determined by ^{19}F NMR spectroscopy *vs* internal standard (4,4'-bis(trifluoromethyl)biphenyl). [b] Regioisomer ratio determined by ^{1}H NMR spectroscopy. [c] Yield of single regioisomer following purification (10:1 r.r. prior to purification, as determined by ^{1}H NMR spectroscopy). Nf, perfluorobutanesulfonyl; DMAP, 4-dimethylaminopyridine; dba, dibenzylideneacetone; BINAP, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; O*m*CB, 3-chlorobenzoate.

Sequential application of our methodology provides modular access to non-symmetrical 3,5-diarylphenols such as **36b** (Fig. 4b), a dimethylated analog of the key building block used in the synthesis of LTB_4 receptor antagonist RO5101576.[65,66] Although the second arylation proceeds without regioselectivity, this approach avoids the formation of symmetrically-arylated side-products that were observed in the original, cross-coupling approach to RO5101576.[65] The overall efficiency of our two-stage sequence is dramatically improved by recovering the bismacycle following the first arylation, and recycling it directly into the second arylation. By isolating the bismacycle again after the second arylation, 84% of this key precursor is recovered for re-use.

In addition to clarifying the origin of experimentally observed reactivity trends, the insight provided by our preliminary mechanistic studies (Fig. 3) also represents a powerful tool to inform the rational design of efficient synthetic strategy (Fig. 4c). For example, the regioisomeric biphenols **37** and **38** can each be prepared with excellent selectivity from a common substrate simply by judicious choice of arylating agent. Thus, whereas use of an electron-rich, benzyloxy-substituted boronic acid affords biphenol **37** following *in situ* deprotection, isomeric biphenol **38** can be accessed selectively by use of an electron-poor hydroxyphenyl precursor that instead enables preferential migration of the phenyl ring. In both cases, the observed selectivity matches that expected from the model illustrated by Fig. 3a; we anticipate that the ability to make *a priori* predictions about selectivity in this way will prove of broad synthetic utility.

Conclusions. We have developed a concise method for the *meta*-selective C–H arylation of polysubstituted phenols, a transformation that cannot be achieved *via* existing methods based on conventional C–H functionalization, EAS, or oxidative coupling. The two-step process of Bi(V)-mediated electrophilic arylation and subsequent 1,2-migration employs readily available reagents, exhibits broad substrate scope and tolerates synthetically useful functionality. Supporting mechanistic studies inform its rational application in synthesis, and provide fundamental insight into the nature of the key migration step.

The regiodiversion strategy presented in this study not only provides access to contiguously substituted phenols featuring contra-electronic substitution patterns, but also represents a more general strategy for the expansion of accessible chemical space. Specifically, we have shown that the regiochemical outcome of EAS need not be limited by the expectations of

established wisdom, and we anticipate that this finding will underpin future advances towards underrepresented benzenoid motifs.

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Author contributions

L.T.B. conceived and directed the project. L.T.B., A.S. and K.R. designed the experiments. A.S. and K.R. carried out the experiments. All of the authors analyzed the data. L.T.B. wrote the manuscript.

Competing interests

The authors declare no competing interests.

Tables

Figure Legends / captions

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Methods

General Procedure for the Synthesis of Cyclohexadienones. A mixture of bismacycle tosylate **S1** (596 mg, 1.00 mmol), $NaHCO_3$ (92.4 mg, 1.10 mmol), and arylboronic acid (1.10 mmol) in

toluene (10 mL) and water (0.50 mL) was stirred at 60 °C until starting material was no longer observed by ^{1}H NMR spectroscopy. The reaction was allowed to cool to rt, aq. NaOH (2.0 M; 2 mL) was added, and the mixture was stirred vigorously for 5 mins. The organic phase was removed, and the remaining aqueous portion was extracted with toluene (2 mL). The combined organic portions were filtered through a pad of $MgSO_4$ (1 cm^3) into a round-bottom flask containing the phenol substrate (1.00 mmol). The mixture was stirred at rt as *m*CPBA (89% purity; 194 mg, 1.00 mmol) was added portion-wise over 5 mins; the reaction was then allowed to stir for a further 30 mins.

Saturated aq. $Na_2S_2O_5$ (1 mL) was added and the resulting mixture was stirred for 5 mins, then water (20 mL) was added. The mixture was extracted with EtOAc (20 mL), the organic portion was washed with sat. aq. Na_2CO_3 (2 × 10 mL), and the aqueous portions were combined and extracted with EtOAc (3 × 10 mL). The combined organic portions were dried over $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The crude product was purified by silica gel column chromatography using the eluent system described for individual compound entries in the Supplementary Information.

General Procedure for 1,2-Aryl Migration / Rearomatization. A flask containing the cyclohexadieneone was evacuated and backfilled with anhydrous dinitrogen three times. Anhydrous toluene ($[cyclohexadieneone]_0$ = 0.10 M) was added and the solution was cooled to 0 °C before trimethylsilyl trifluoromethanesulfonate (1.0 eq.) was added dropwise *via* syringe over 5 mins. The ice bath was removed and the reaction was allowed to warm to rt over 18 hours. Sat. aq. $NaHCO_3$ (5 mL) was added, the mixture was stirred for 15 mins, then the aqueous phase was removed and extracted with EtOAc (3 × 10 mL). The combined organic

portions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Where further purification was required, the appropriate procedure is described for individual compound entries in the Supplementary Information.

Data availability

The authors declare that all data supporting the findings of this study are available within the paper and its Supplementary Information files.